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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,656	SCHULTE ET AL.	
	Examiner	Art Unit	
	Kevin K. Hill, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-28,31,46 and 48-54* is/are pending in the application.

4a) Of the above claim(s) *14-18,23 and 55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-13,19-22,24-28,31,46 and 48-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 October 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. Applicant's response to the Requirement for Restriction, filed on October 29, 2007 is acknowledged. Applicant has elected without traverse the invention designated as Invention Group II, claims 2-31 and 46, directed to a method of using a composition comprising one or more double-stranded oligoribonucleotides (dsRNA) for the specific modulation of the expression of target genes in cells and/or tissues of the CNS and/or eye, wherein said composition is introduced into a cell, tissue or organism outside the blood-brain or blood-retina barrier.

Within Group II, Applicant has further elected the restricted neural tissue subgroup, cells and tissues of the eye.

Within Group II, Applicant has elected the following species:

i) wherein the dsRNA molecule is dsRNA molecules between 21 and 23 nucleotides in length, as recited in claim 13,

ii) wherein the promoter is a tissue specific promoter, as recited in claim 20,

iii) wherein the dsRNA is complexed to a micellar structure, as recited in claim 22,

iv) wherein the means by which the dsRNA is administered to the eyeball systemic administration, as recited in claim 26,

v) wherein the eye disease is a degenerative retinal disease, as recited in claim 50, and

vi) wherein the organism is human, as recited in claim 31.

Because Applicant did not distinctly and specifically point out the supposed errors in the Group or species restriction requirement, the election has been treated as an election without traverse and the restriction and election requirement is deemed proper and therefore made final (MPEP § 818).

Amendments

In the reply filed October 29, 2007, Applicant has cancelled Claims 1, 29-30, 32-45, 47, amended Claims 5-28, 46, and added new claims, Claims 48-55. Applicant's new claims have

been entered into the application as requested and will be examined on the merits herein, as they are considered to belong to the elected group.

Claims 14-18, 23 and 55 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 2-13, 19-22, 24-28, 31, 46 and 48-54 are under consideration.

Priority

2. This application is a 371 of PCT/EP03/04002, filed April 18, 2002. Applicant's claim for the benefit of a prior-filed application parent provisional application 60/431,173, filed December 5, 2002, under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

Acknowledgment is made of Applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). While a certified copy of the foreign patent application EPO 02008671.5, filed April 18, 2002, has been filed with the instant application, a certified English translation has not been provided.

The effective priority date of the instant application is granted as April 18, 2002.

Information Disclosure Statement

Applicant has filed Information Disclosure Statements on January 21, 2005, December 12, 2005 and February 26, 2007. The Examiner was able to consider these to the extent of time allowable. These have been considered. The signed and initialed PTO Forms 1449 are mailed with this action.

Drawings

3. **New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because** Figure 1 comprises eight panels, none of which are labeled. Furthermore, the upper panels do not photocopy well and are essentially opaque, thus prohibiting the Examiner from evaluating the data on its merits. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no

longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Specification

4. **The disclosure is objected to because of the following informalities:** Figure 1 contains eight panels. However, the instant specification (pg 22) does not disclose the identity of the panels, nor correlate their respective relationships. The Examiner respectfully suggests amending the figure to label the panels, e.g. A-H, as well as the specification's figure legend (pg 22).

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the Applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.

(b) CROSS-REFERENCE TO RELATED APPLICATIONS.

(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.

(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.

(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.

(f) BACKGROUND OF THE INVENTION.

(1) Field of the Invention.

(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.

(g) BRIEF SUMMARY OF THE INVENTION.

(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).

(i) DETAILED DESCRIPTION OF THE INVENTION.

(j) CLAIM OR CLAIMS (commencing on a separate sheet).

(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).

(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Appropriate correction is required.

Claim Objections

5. **Claims 20 and 26 are objected to because of the following informalities:**

With respect to claim 20, the phrase "the expression said dsRNA" on line 2 is missing the preposition "of", as in "the expression of said dsRNA".

With respect to claim 26, the phrase "is in form" on line 2 is missing the article "a", as in "is in a form".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. **Claims 2-13, 19-22, 24-28, 31, 46 and 48-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.** The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to a method for the specific modulation of the expression of an enormous genus of target genes in cells and/or tissues of the eye, wherein a composition comprising one or more of an enormous genus of structurally distinct double-stranded oligoribonucleotides (dsRNA) is introduced into a cell, tissue or organism outside the blood-brain or blood-retina barriers. The intended use of the method is for the therapeutic treatment of diseases related to the eye (pg 2, ¶4; pg 4, lines 3-4).

At issue for the purpose of written description requirements are:

a) the identity of the target gene-specific dsRNA target domain(s) oligoribonucleotide molecules capable of inhibiting the expression of the enormous genus of desired target gene(s), and

b) the essential features of the composition formulations that distinguish such formulations from other art-recognized purposes or modes of delivery that i) avoid side effects outside the target organs eye and brain, and ii) achieve both efficient and sufficient target specificity which would minimize the risk of unwanted side effects of systemic application—to wit, the art-recognized problems disclosed to have been solved by the present invention, thereby achieving the **specific inhibition** of the enormous genus of target genes expressed in the eye.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

Adequate written description support does not exist in the instant application for the breadth of the claimed method because neither the instant application nor the prior art adequately describe a representative number of dsRNA target domains of an enormous genus of desired target genes, the abnormal expression of which has been clearly correlated with the countless number of eye disorders embraced by the claims nor adequately describe the particular features

or distinguishing characteristics common to genes that are related to or correlated with the multitude of eye disorders treatable by the instant method. As a result, Applicant has not described the target genes to be targeted by the instant method using inhibitory dsRNA. Logically, if neither the instant application nor the prior art enables one of skill in the art to instantly recognize the dsRNA target domains of the enormous genus of target genes to be silenced by the instant method, Applicant has not described the genus of dsRNAs necessary to treat all the disorders embraced by the claims. Therefore, Applicant has not demonstrated they were in possession of the genus of methods now claimed. The Examiner is unable to readily find any disclosure in the instant application or prior art nor any evidence in the case record establishing the correlation between a representative number of target genes and the treatment of the genus of eye disorders (pgs 6-7, joining ¶), wherein the target gene is of particular relevance to retinal detachment, juvenile retinoschisis, age-related macular degeneration (AMD) in the eye, for example. Such disorders are expected to involve a complex array of genes and genetic factors (pg 7, ¶2), and the specification fails to identify the gene(s) responsible or provide any guidance as to which genes in particular should be targeted to treat the claimed retinal degeneration diseases.

With respect to the enormous genus of structurally distinct dsRNA oligoribonucleotide molecules specific for an enormous genus of structurally distinct target genes expressed in the eye and/or CNS, the dsRNAs required for the methods are recited in terms of their function only, there is no art-recognized correlation between their structure and their required function (treatment of eye disorders), and the specification does not provide the support needed to enable one skilled in the art to predict with a reasonable degree of confidence the structure of the dsRNAs from a recitation of function alone. What is needed is a description of the target genes that have been clearly correlated with the eye disorders that may be treated by the instantly claimed methods.

> *Vas-cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification

should "clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See *Vas-cath* at page 1116).

The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see *In re Shokal* 113USPQ283(CCPA1957); *Purdue Pharma L.P. vs Faulding Inc.* 56 USPQ2nd 1481 (CAFC 2000). In the instant case, the specification discloses a dsRNA molecule specific for the target gene encoding enhanced Green Fluorescent Protein (eGFP). However, the use of an eGFP-specific dsRNA and an eGFP target gene is an experimental system, and no retinal disease is present in the model. Furthermore, there is no correlation between the expression of eGFP and retinal disease. Thus, these single eGFP-specific dsRNA molecule and eGFP target gene species do not adequately represent an enormous genus of structurally distinct dsRNA oligoribonucleotide molecules nor an enormous genus of structurally distinct retinal disease target gene, wherein the dsRNA molecules inherently possess sufficient target specificity to avoid side effects (pg 5, line 16). More specifically, one of skill in the art would not be able to envision the structure of any dsRNA molecule or target gene nucleic acid or any modified variants thereof that would enable one of skill to practice the instant invention because the instant application does not describe any such nucleic acids.

With respect to the formulations disclosed to have been solved by the present invention, adequate written description support does not exist for the methods now claimed because neither the instant application nor the prior art adequately describes a sufficient number of compositions nor provides any description of the features or makeup common to the genus of compositions designed to be applied outside the blood-retina barrier, e.g. systemic, iontophoretic administration, or retrobulbar application for treatment of the disorders now embraced by the claims. The specification discloses the intravenous (systemic) or retrobulbar (local) injection of naked eGFP-specific dsRNA molecules formulated at 200μg/kg body weight in buffer (pg 26, line 7). Applicant claims a genus of compositions and administration method steps designed to overcome the stringent activity of the blood-brain and/or blood-retina barrier so as to efficiently

and sufficiently deliver significant quantities of active dsRNA with sufficient target specificity to overcome side effects outside the target organs (eye and/or CNS) that has plagued administration methods of the prior art (pg 5, lines 16-22) without specifically describing what those compositions look like. The model transgenic mouse strain disclosed in the specification expresses GFP in multiple neural and non-neural tissues, e.g. retina, brain, kidney, testis, lung and spleen (Mothe et al, J. Histochem. & Cytochem. 53(10):1215-1226, 2005; pg 1220, Table 1). However, the instant specification does not disclose whether the systemic administration of naked dsRNA in buffer would, in fact, inherently avoid side effects outside the target organs eye and brain, and achieve both efficient and sufficient target specificity which would minimize the risk of unwanted side effects of systemic application because the specification only discloses results achieved in the retina. No analysis of other eGFP-expressing tissues, and their relative gene-silencing effects as compared to the target eye tissue, respectively, is disclosed. Thus, the eye-specific inhibition of target gene expression has not been demonstrated. Neither the application nor the prior art provides any description that would enable one of skill to distinguish the instantly recited composition formulation from any other composition formulation designed for any other purpose or mode of delivery practiced in the art. There is no demonstration in the prior art nor the instant specification that systemic administration of naked dsRNA would specifically target the dsRNA to the eye, as opposed to other tissues in the body. Thus, Applicants are essentially inviting the skilled artisan to experiment and identify such composition formularies and administration method steps empirically that would efficiently and specifically deliver the dsRNA to the eye while simultaneously efficiently avoiding unwanted side effects in other tissues that also express the target gene. It is clear that the compositions needed to practice the instant methods must be suitable for delivery outside the blood-retina barrier, but Applicants have not described the particular features or properties common to those compositions.

The Revised Interim Guidelines state:

"The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and

which is not conventional in the art" (col. 3, page 71434), "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus", "in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (col. 2, page 71436).

An Applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

Possession may also be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the Applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 1 19 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998), *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)*, *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See *Fiers v. Revel*, 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. *In Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

> Without a correlation between structure and function, the claim does little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. *See Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 ("definition by function ... does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is").

Applicant has not provided any description or reduction to practice of a method for the specific modulation of the expression of target genes in cells and/or tissues of the eye, wherein the target gene is responsible for the genus of retinal diseases embraced by the claims. Based on the Applicant's specification, the skilled artisan cannot envision the detailed chemical structure of the dsRNA nucleotide sequences which would be necessary to hybridize and actuate post-transcriptional gene silencing of those target genes responsible for diseases in the eye. The instant application discloses no correlation between the structures of the genus of target genes and the genus of eye disorders. Thus, Applicant has not demonstrated possession of the genus of dsRNAs needed to practice the instant methods.

Further, Applicants have not demonstrated possession of the genus of composition formulations designed particularly for the mode of administration now required because Applicants have not described the features distinguishing such compositions from all other compositions nor that the contemplated formulations do in fact achieve both efficient and sufficient target specificity which would minimize the risk of unwanted side effects of systemic application outside the target organs eye and brain—the problem disclosed to have been specifically solved by the inventors. The composition formulations are claimed in terms of their intended uses only with no description of how the intended use relates to the physical and chemical characteristics of the compositions themselves.

While the specification discloses that dsRNA targeting GFP may be delivered to the retina of a transgenic mouse via intravenous or retrobulbar injection and that GFP expression in the retina may be reduced (pgs 23-25), this example is not directed to the treatment of any eye or

CNS disorder and does not describe any dsRNA or siRNA or any vector thereof, nor any other molecule for use in the instant methods to treat an eye or CNS disorder.

MPEP §2163 states, in part: "[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when . . . the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed. In re Curtis, 354 F.3d 1347,1358,69 USPQ2d 1274, 1282 (Fed. Cir. 2004)."

In the instant case, while genes may indeed be suitable targets for a given disorder, even if one knew which gene was related to any given disorder and whether or not to inhibit or agonize the gene or gene product, one of skill in the art would, nevertheless, be left to *de novo* screening methods to identify the dsRNAs having the desired activity to produce the desired therapeutic effect. Applicant acknowledges that "[D]ue to the complexity of the clinical phenotype, it may be assumed that the number of genes is large, which, when mutated contribute to AMD susceptibility." (pg 8, lines 8-10). However, neither the specification nor the prior art teaches the identity of these genes.

Thus, for the reasons outlined above, it is concluded that the claims do not meet the requirements for written description under 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

7. **Claims 2-13, 20-22, 24-28, 31, 46, 48-49 and 51-54 are rejected under 35 U.S.C. 112, first paragraph**, because the specification, while being enabling for a method for inhibiting the expression of enhanced Green Fluorescent Protein (eGFP) in the eye, wherein a composition comprising one or more naked eGFP-specific double-stranded RNAs (dsRNA) and buffer is introduced systemically by intravenous administration or locally by retrobulbar injection into an organism, does not reasonably provide enablement for methods of increasing the expression of an enormous genus of target genes in the eye, inhibiting the expression of an enormous genus of

target genes comprising the administration of a composition comprising one or more of an enormous genus of structurally distinct dsRNA molecules, nor treating an enormous genus of eye disorders by targeting an enormous genus of genes expressed in the eye, wherein the composition comprising one or more structurally distinct double-stranded RNAs (dsRNA) formulated in an enormous genus of carriers such as liposomes, plasmids, coat proteins, or fusogenic peptides, is introduced by a genus of physiologically distinct administration routes into a cell or tissue outside the blood-brain or blood-retina barriers.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

The claims are broad because the term "modulation" embraces both increasing and decreasing the expression of the target gene,

The claims are broad because the method may be performed *in vitro* and *ex vivo* (both of which are "outside the blood-brain or blood-retina barriers", as well as *in vivo*.

The breadth of the claims is exceptionally large for encompassing an enormous genus of undisclosed and structurally distinct dsRNA compositions that are capable of inhibiting the expression an enormous genus of structurally distinct target genes in the eye.

The breadth of the claims is exceptionally large for encompassing an enormous genus of composition formularies, e.g. naked dsRNA, liposomal carriers thereof, nucleic acid vectors expressing dsRNA, and liposomal carriers thereof, as well as gene therapy and cell-based therapy.

The breadth of the claims in combination with the fact that the specification discloses the intended use of the dsRNA in the method is for the therapeutic treatment of an enormous genus of etiologically and pathologically distinct diseases related to the eye (pg 2, ¶4; pg 4, lines 3-4) by "modulating a target gene" requires that these claims be evaluated to determine whether the specification provides teaches how to use these compositions and perform the claimed method for treating these conditions by modulating, i.e., increasing and decreasing, the expression of a target gene.

The claims are also broad for encompassing an enormous genus of animal organisms comprising a central nervous system and/or eyes, about 1,000,000 species of vertebrate and invertebrate animals (waynesword.palomar.edu/trfeb98.htm, last visited November 26, 2007), whereupon the enormous genus of eye diseases may be treated as per the claimed invention.

When the claims are analyzed in light of the specification, the inventive concept in the instant application is that dsRNA molecules of a length of 21 to 23 nucleotides are capable of, after systemic application, e.g. intravenous injection, or by retrobulbar injection, to cross the blood-retina barrier (pg 17, ¶3).

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

The breadth of the claims requires evaluating the specification for enabling disclosure teaching one of skill how to use dsRNAs to inhibit the expression of a gene to treat the complete

genus of disorders now embraced by the claims. That is, it is imperative that the specification or the prior art have taught one of skill at the time of filing how to correct the genus of eye disorders by inhibiting the expression of specific genes, gene families, or classes, which may be overexpressed or expressed as mutant isoforms sensitive to the effects of interference by dsRNA. One of skill would have needed to know which genes to target in order to effectively treat the disorder without undue experimentation. However comprehensive disclosure enabling one of skill to practice the full scope of the instant methods without undue experimentation is lacking.

The specification discloses that systemic application of double-stranded RNAs, also known in the art as small interfering RNAs (siRNA) generally gives rise to side effects outside the target organs eye and brain-often without significant quantities of active substance being detectable in the target tissue. Even with sufficient target specificity, which would minimize the risk of unwanted side effects of systemic application, this method of application remains inefficient, since the target tissue and target cells are located beyond the blood-brain or blood-retina barrier and the active substance is not able to reach its site of activity because of the stringent activity of this barrier. This problem has been solved by the present invention (pg 5).

Applicant contemplates the nucleic acids may be introduced into the cells or tissues bound to other molecules and/or combined with one or more suitable carriers, e.g. liposomes, coat proteins, and fusogenic peptides (pg 13, ¶1). The compositions of the invention may be administered locally, e.g. iontophoretically or by retrobulbar injection, or systemically, e.g. intravenously, subcutaneously, intrasynovially, or orally (pg 18, ¶2) at concentrations ranging between about 0.001μg to about 10mg units/day and/or units/kg body weight (pg 6, ¶3; pg 18, lines 1-6), wherein the dsRNA molecules inhibit the corresponding target gene(s) by post-transcriptional silencing.

"The central idea of the present invention is surprising in so far as dsRNA molecules of a length of 21 to 23 nucleotides are able to cross the blood-retina barrier, and specifically inactivate target genes in the tissues of the back of the eye, after systemic application, for example by intravenous injection. This overcoming the blood-retina barrier is all the more remarkable, because no experiment could demonstrate overcoming this barrier by dsRNA so far." (pg 12, lines 1-6). "The method described in this invention is distinguished from the prior

art by the fact that it could be shown for the first time that dsRNA molecules, preferably of the length specified above, can be detected inside the eye after systemic or local application outside the eyeball." (pg 13, ¶2).

The working examples disclose that systemic administration by tail vein injection or local administration by retrobulbar injection of 200μg/kg of naked dsRNA in buffer targeted against an enhanced GFP transgene appears to be capable of inducing post-transcriptional gene silencing of the eGFP in the retina and retinal pigment epithelial cells in a mouse model.

The Examiner notes that while Experimental Procedures 2 and 4-5 appear to be designed to determine the optimal time of efficacy of post-transcriptional gene silencing, neither the specification nor the table disclose the result obtained--the optimal time of efficacy of post-transcriptional gene silencing. Similarly, while Experimental Procedure 3 appears to be designed to determine the optimal dsRNA concentration for post-transcriptional gene silencing, the table indicates only the use of 200μg/kg. Thus, the concentration variable was not even manipulated and compared to other concentrations as indicated by the preamble. Furthermore, neither the specification nor the tables disclose the result obtained-- the optimal dsRNA concentration for post-transcriptional gene silencing (pgs 28-30).

The specification is not enabling because while the instant application provides working examples teaching one of skill how to deliver dsRNA to into cells in the eye of subject to inhibit the expression of a target gene in the cell by post-transcriptional gene silencing, the instant application fails to provide any disclosure showing how the administration of dsRNA may **increase** the expression of a gene in a cell in the eye, which is embraced by the limitation "capable of modulating a target gene" in claim 2. Further, a review of the prior art fails to find any evidence that dsRNAs of 21 to 23 nucleotides may specifically increase the expression or activity of a gene to treat an eye disorder.

Given the absence of such disclosure, the skilled artisan would not know a *priori* whether introduction of dsRNAs *in vivo* by the broadly disclosed methodologies of the instant invention, would result in the agent reaching the proper cell in a sufficient concentration and remaining for

a sufficient time to increase the expression of a target gene. Neither the specification nor the prior art provide the guidance necessary to teach one of skill how to increase the expression of a gene using dsRNA, and there is no evidence in the prior art or specification to even suggest that dsRNA is capable of such activities. Rather, a careful reading of the specification shows that Applicant's invention is directed to the inhibition of gene expression not enhancing gene expression. The latter is conventionally accomplished by expressing the full length gene not by administering short interfering RNA.

The specification is not enabling because neither it nor the prior art enable one of skill to practice the full scope of the methods now claimed without undue experimentation. The specification does not teach the enormous genus of genes specifically overexpressed or aberrantly expressed, i.e., as mutant isoforms in the complete genus of eye disorders of the enormous genus of animals encompassed by the claims, and how such expression is specifically related to the eye disorders embraced by and specifically recited in the instant claims. Such information is essential to the practice of the instant methods. While the specification provides enabling disclosure for delivering dsRNA into a mammalian (mouse) eye by administration outside the blood-retina barrier, the specification is not considered to be enabling for treating all possible eye disorders in the enormous genus of animals possessing eyes. Given the complexity of the biochemistry of such disorders, the distinctly different anatomical properties that comprise blood-retina barriers, and the many genes expressed in the eye which may or may not be directly related to the disorders, one of skill would require specific guidance as to how to design the dsRNAs effective for inhibiting the expression of a gene involved in any disorder in order to treat the disorder. Such comprehensive disclosure is lacking.

The specification is not enabling because it does not disclose those formulations and nucleic acid molecule concentrations necessary to overcome the art-recognized unwanted side effects outside the target organs eye and brain-often without significant quantities of active substance being detectable in the target tissue. The disclosed target gene, eGFP, is an exogenous gene, and thus does not reflect the existence of unwanted side effects caused by the expression of a developmentally important gene.

The State of the Prior Art, The Level of One of Ordinary Skill and The Level of Predictability in the Art

dsRNA

The instant claims encompass the pharmaceutical use of the oligonucleotide compositions and formulations of the instant invention for treatment purposes. However, the specification as filed does not enable one skilled in the art to use the claimed pharmaceutical compositions or formulations for treatment purposes *in vivo.* In regards to the amount of direction or guidance presented, the specification as filed does not provide sufficient guidance or instruction that would teach one of skill in the art how to successfully practice a therapeutic method to treat a retinal degeneration disease or eye condition associated with the expression of a particular mRNA target, comprising the administering to a patient the double-stranded RNA compositions and formulations according to the present invention.

Regarding the level of predictability or unpredictability associated with the antisense therapeutic art, Crooke (Progress in Antisense Technology, in Methods of Enzymology 313:3-45, 1999, Academic Press), states "extrapolations from in vitro uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man [that] demonstrate that, even after careful consideration of all *in vitro* uptake data, one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies [references omitted]." Furthermore, Crooke describes a variety of factors that influences the activity of antisense-based compounds. Crooke teaches that variations in cellular uptake and distribution of antisense oligonucleotides are influenced by a variety of factors: length of oligonucleotide, modifications, and sequence of oligonucleotide and cell type. The influence of non-antisense effects, for example phosphorothioate oligonucleotides tend to bind non-specifically to many proteins, wherein such protein binding influences cellular uptake, distribution, metabolism and excretion of said oligonucleotide. Additionally, non-specific protein binding may produce effects that can be mistakenly interpreted as antisense activity, and may also inhibit antisense activity of some oligonucleotides. In addition to proteins, oligonucleotides may non-specifically interact with other biological molecules, such as lipids, or carbohydrates, wherein the chemical class of oligonucleotide will influence such interactions

studied (Crooke, 1999; p. 3). Crooke clearly teaches that there is a significant level of factors which influence the behavior of antisense based compounds thereby rendering the activity of antisense compounds unpredictable.

Caplen (Caplen, N.J., August, Gene Therapy 11(16): 1241-1248, 2004) reviews the progress and prospects of RNA interference methods triggered by double-stranded RNA. While RNAi appears to be easy to induce, critical analysis of RNAi derived phenotypic data should not be overlooked. The validation of the RNAi effect in mammalian cells is important and that non-specific effects of RNAi need to be carefully assessed in mammalian cells (pg 1245). For example, "ensuring the specificity and quantifying the efficacy of the particular siRNA or shRNA against a clinically relevant target transcript is essential in justifying its further development." And, Caplen states "it should be possible to rescue the functional phenotype induced by RNAi by expression of a transcript resistant to the siRNA under study."

Caplen addresses the degree of unpredictability in the art when choosing a biologically effective antisense sequence, stating that "it is unclear at this time (2004) what the minimum level of homology required between the siRNA and the target to decrease gene expression is, but it has been reported that matches of as few as 11 consecutive nucleotides can affect the RNA levels of a non-targeted transcript" (pg 1245, col. 2). This is especially relevant in mammalian cells because mammalian cells have nonspecific dsRNA-triggered responses primarily mediated through interferon-associated pathways that are absent in invertebrates and plants. Caplen expresses the importance in recognizing that there is variation in the degree of inhibition mediated by different small interfering RNA sequences which may result in the production of different phenotypes.

Delivery

In regards to the delivery of oligonucleotide pharmaceutical compositions *in vivo*, the state of the art indicates that delivery of these oligonucleotide compositions for therapeutic purposes "remains an important and inordinately difficult challenge (Chirila et al, January, Biomaterials 23:321-342, 2002, see abstract)." At the time of filing of the instant application there were no general guidelines for successful *in vivo* delivery of antisense compounds known

in the art. Problems related to the pharmaceutical use of nucleic acids in general, and antisense and siRNA nucleic acids in particular, are evident from the pre- and post-filing art. One problem is the inability to routinely deliver an effective concentration of a specific nucleic acid into a target cell, such that a target gene or miRNA is inhibited to a degree necessary to produce a therapeutic effect--in this case inhibition of RNA silencing of a gene.

Opalinska et al (Nature Reviews 1:503-514, 2002) teach that: "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA". "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded." (page 511, columns 1-2)

Lu et al (RNA Interference Technology, Cambridge, Appasani, ed., 2005, page 303) state that "Unlike *in vitro* transfection of siRNA into cells, *in vivo* delivery of siRNA into targeted tissue in animal models is much more complicated, involving physical, chemical and biological approaches, and in some cases their combination." Therapeutic applications, however, clearly depend upon optimized local and systemic delivery of siRNA *in vivo*. "....limited reports of *in vivo* studies have indicated a lack of effective delivery methods for siRNA agents." "...the two most critical hurdles are maintaining its [siRNA] stability *in vivo* and delivery to disease tissues and cells." (page 314) Lu et al. admit that while hydrodynamic delivery of siRNA duplexes into mouse liver has proven to be quite efficient, this technique is not clinically feasible in human studies.

Sioud (RNA Silencing, Methods and Protocols, Humana Press, 2005) expresses similar reservations, specifically with respect to the use of cationic carriers, as currently claimed in

claims 34 and 35. On page 238, Sioud states "Despite some encouraging results, however, liposomes still have not the characteristics to be perfect carriers because of toxicity, short circulation time, and limited intracellular delivery for target cells." And on page 243, "The *in vivo* uptake of siRNAs can differ dramatically with cell types as well as with the status of cell differentiation."

Similarly, Simeoni et al (RNA Silencing, Methods and Protocols, Humana Press, 2005, page 251) state "So far, although siRNA transfection can be achieved with classical laboratory-cultured cell lines using lipid-based formulations, siRNA delivery remains a major challenge for many cell lines and there is still no reasonably efficient method for *in vivo* application."

Gene Therapy

Applicant contemplates that the recombinant nucleic acid composition may be encoded by a vector, and thus Applicant's invention falls within the realm of gene therapy, which is in the nature of transforming cells with nucleic acids encoding therapeutic molecules to produce a therapeutic effect. The claims are drawn to a method for inducing RNA-associated gene silencing effects, wherein the dsRNA will effect post-transcriptional gene silencing of a target gene in a cell or tissue *in vitro* or *in vivo*.

With regard to gene therapy, at the effective filing date of the present application, May 18, 2002, the attainment of any therapeutic effect via gene therapy was, and remains, highly unpredictable, let alone for the attainment of prophylactic effects via gene therapy mechanisms as contemplated by Applicants. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be a difficulty as supported by numerous teachings available in the art. There are several known factors that limit an effective human gene therapy, including sub-optimal vectors, the lack of a stable *in vivo* transgene expression, the adverse host immunological responses to the delivered vectors and most importantly an efficient gene delivery to target tissues or cells. For example, Deonarain (Deonarain, M., Expert Opin. Ther. Pat. 8:53-69, 1998) indicates that:

> "[O]ne of the biggest problems hampering successful gene therapy is the ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph).

Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (page 65, CONCLUSION). Verma and Somia (Nature 389: 239-242, 1997) review vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Verma states that:

> "the Achilles heel of gene therapy is gene delivery and this is the aspect we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression . . ."

The use of viruses (viral vectors) is a powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells. However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses (e.g., p. 239, col. 3). Even in 2005, Verma and Weitzman (Annu. Rev. Biochem. 74:711-738, 2005) still state:

> "The young field of gene therapy promises major medical progress toward the cure of a broad spectrum of human diseases, ranging from immunological disorders to head disease and cancer. It has, therefore, generated great hopes and great hypes, but it has yet to deliver its promised potential", and "[I]f scientists from many different disciplines participate and pull together as a team to tackle the obstacles, gene therapy will be added to our medicinal armada and the ever- expanding arsenal of new therapeutic modalities." (page 732, top of third paragraph).

Goncalves (BioEssays 27:506-517, 2005) also states:

"Overall, one can conclude that further improvements in gene transfer technologies (e.g. control over transgene expression and integration) and deeper insights in host-vector interactions (e.g. knowledge on vector and gene-modified cell biodistribution following different routes of administration and the impact on innate and adaptive immunity) are warranted before clinical gene therapy reaches maturity" (page 514, right-hand column, last paragraph).

Gardlik et al (Med. Sci. Monit. 11:RA110-121, 2005) conclude:

"Although clinical trials have already started, there are still numerous limitations that must be solved before routine clinical use. Nevertheless, it can be expected that future research will bring tissue- and disease-specific delivery strategies and that this hurdle will be overcome at last" (page RA119, right-hand column, last paragraph).

Such problems with delivery continue to plague the field of gene therapy. Shoji et al. has characterized the current state of the art as the "tragic failure of gene therapy" because of poor delivery of gene based medicines due to the lack of an appropriate vector that "fulfills the necessary requirements, including high transfection efficiency, non toxicity, non-pathogenicity, non-immunogenicity, [and] non-tumorgenicity." (Shoji et al, Current Pharmaceutical Design 10(7): 785-796, 2004).

Summary

The efficacy of antisense-based therapies hinges upon the ability to deliver a sufficient amount of oligonucleotide to the appropriate tissues and for a sufficient period of time to produce the desired therapeutic effect. Even though the level of skill in the art was high, being that of a Ph.D. or M.D., the artisan would find the art to be generally of a low level of predictability for the use of dsRNAs, alone or encoded in expression vectors, for the treatment of any disorder. So far, it appears that all of the developments in nucleic acid-based therapies have not been sufficient to overcome this one basic obstacle—drug delivery. The art teaches that the behavior of oligonucleotide-based compositions and their delivery *in vivo* are unpredictable,

therefore claims to pharmaceutical compositions and methods of treating diseases by the administration of oligonucleotide-based pharmaceuticals are subject to the question of enablement due to the high level of unpredictability associated with this technique as taught in the prior art.

In view of the express teachings of the post-filing art suggesting that *in vivo* delivery of dsRNA, by itself or encoded in an expression vector, is unpredictable, it is essential that the instant application provide enabling disclosure showing how to use the pharmaceutical compositions of the instant invention to target any desired gene in any cell in any animal to effect the desired outcome. The skilled artisan would not know *a priori* whether introduction of oligonucleotides *in vivo* by the broadly disclosed methodologies of the instant invention, would result in the oligonucleotide crossing the enormous genus of anatomically and physiologically distinct blood-brain and/or blood-retina barriers to reach the desired retinal cell in the enormous genus of anatomically distinct animals in a sufficient concentration and remaining for a sufficient time to activate target-specific RNA interference of any desired gene. Specific guidance would be required to teach one of skill in the art how to deliver double-stranded RNA molecules to cells *in vivo* to produce a measurable effect in an organism. The state of the art is such that successful delivery of dsRNA *in vivo* or *in vitro* such that the oligonucleotide provides the requisite biological effect to the target cells/tissues/organs must be determined empirically.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

The quantity of experimentation required to practice the invention as claimed, based upon what is known in the art and what has been disclosed in the specification, will create an undue burden for a person of ordinary skill in the art because it would require the artisan to experiment to identify the target gene responsible for any one of an enormous genus of etiologically and pathologically distinct retinal diseases, determine the structures of the mRNA targets that are associated with a particular condition or disease for which therapy is sought, determine the dsRNA nucleic acid sequence(s) that would specifically actuate post-transcriptional gene silencing of the target gene, determine those vectors and expression control elements that could be used to efficiently express the dsRNA in the desired retinal cell type, and identify modes of

delivery *in vivo* such that the expression of desired target gene is inhibited at a significant level and for a sufficient amount of time to produce the desired therapeutic effect so as to treat the enormous genus of retinal diseases in the enormous genus of animals. Neither the specification as filed, nor the prior art searched, provides any specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

In conclusion, the specification fails to provide any guidance as to how an artisan would have dealt with the art-recognized limitations of the claimed method commensurate with the scope of the claimed invention and therefore, limiting the claimed invention to a method for inhibiting the expression of a target gene in the eye, wherein a composition comprising one or more naked double-stranded RNAs (dsRNA) is introduced systemically by intravenous administration into an organism, is proper.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

8. **Claims 2-13, 19-22, 24-28, 31, 46 and 48-54 are rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

With respect to claim 2 (and dependent claims), the claims are vague in that no step(s) in the claimed method refers back to or recapitulates the preamble of the claim. Applicants recite a method for the specific modulation of the expression of target genes in cells and/or tissues of the eye, wherein a composition comprising one or more double-stranded oligoribonucleotides (dsRNA) is introduce into a cell, tissue or organism outside the blood-brain or blood-retina barrier, but no step is recited that actually accomplishes the preamble. It is unclear if additional,

undisclosed steps are a part of the claimed method and therefore the metes and bounds of the claimed subject matter are unclear.

With respect to claims 3 and 26, the claims recite the term "preferably" in reference to the method step of maintaining the test cell, tissue and/or organism or administering the composition. However, it is unclear how the artisan's preference would or would not infringe upon the claimed invention because preferences are subjective cognitive perspectives, not an active method steps.

With respect to claim 8, the limitation "inner segment of the eye ball" is unclear because the eye ball is a sphere comprising an inner surface, an outer surface and distinctly different tissues along different coordinates of the sphere. Neither the claims nor the specification defines "inner segment of the eye ball" so as to clearly distinguish the cells and/or tissue of one part of the eye ball from another part of the eye ball.

With respect to claims 11 and 12, the limitations "predominantly expressed" or "specific for" in a cell and/or tissue is unclear because the referenced cell and/or tissue that establishes the basis for the limitation is not disclosed in either the claims or the specification.

With respect to claim 20, there is insufficient antecedent basis for the limitation "the expression said dsRNA" because claim 2, from which claim 20 depends, recites a composition comprising dsRNA, not a composition that expresses dsRNA. It appears that claim 20 would more properly depend on claim 19, "wherein the dsRNA molecules are encoded by a vector".

With respect to claim 25, the claim requires the carrier to be specific for a cell or tissue recited in claims 7-12. However, claims 11-12 do not recite further limitations of a cell or tissue recited in independent claim 2, and thus it is unclear how the cell or tissue of claim 25 is further distinguished from claim 2. Furthermore, the claim is indefinite since neither the claims nor the specification define those features which would distinguish the specificity of the carrier from that disclosed in claim 21, which is a "suitable carrier".

With respect to claim 26, the claim requires the composition be administered "in a form designed to be applied outside the eye ball". The scope and meaning of the limitation "a form designed to be applied outside the eye ball" is defined neither by the claims or the specification in a manner that would adequately apprise one of skill as to which compositions are specifically

included or excluded by the claims. As a result, the metes and bounds of the claims as a whole are unclear. For example, the specification does not enable one of skill to distinguish between compositions designed to be applied outside the eye ball from those not designed to be applied outside the eye ball or from those designed to be applied inside the eye ball. The specific differences and distinguishing characteristics are not defined. As a result, it is unclear how the subject matter of the claim is specifically distinguished from that of claim 2, from which it depends.

Appropriate correction and/or clarification is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the Applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the Applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. **Claims 2, 7, 13, 21-22, 24-28, 31 and 54 are rejected under 35 U.S.C. 102(b)** as being anticipated by Carter (U.S. Patent No. 5,712,257).

With respect to claim 2, Carter discloses a method for the specific modulation of the expression of target genes in cells and/or tissues of the eye, wherein a composition comprising one or more double-stranded oligoribonucleotides (dsRNA) is introduce into a cell, tissue or organism outside the blood-brain or blood-retina barrier.

With respect to claim 7, 24 and 26, Carter discloses that the art has practiced administering dsRNA by injection into a patient's bloodstream (col. 1, lines 37-38) and that the

composition may also be topically administered (col. 7, line 1), in a form to be applied outside the eyeball, e.g. eye drops (col. 7, line 34). Thus, the carrier and/or dsRNA-binding molecules were selected such that the dsRNA molecules are delivered continuously to the target cells or tissues over a defined period of time.

With respect to claim 13, Carter discloses the dsRNA may be between 21-23 nucleotides in length (col. 7, line 51-col. 8, line 14).

With respect to claims 21-22, Carter discloses the dsRNA is complexed with a surfactant forming a micelle (col. 1, lines 55-56), wherein the surfactant may be anionic, cationic or non-ionic (col. 1, lines 63-64; col. 3, lines 20-42).

With respect to claim 25, Carter discloses the ternary complex may further comprise a component that provides specific tropism or attraction for a certain cell class (col. 4, lines 55-63).

With respect to claims 27-28 and 31, Carter discloses the cells, tissue or organism may be mammalian, e.g. mouse or human (col. 3, line 18; col. 6, line 33; col. 7, line 17; col. 8, line 43), wherein one of ordinary skill in the art recognizes mammals to be vertebrates.

With respect to claim 54, Carter discloses the dsRNA may be complexed with liposomes (col. 13, lines 49-50).

10. **Claims 2-3, 5-10, 13, 19-22, 24-28, 31, 46 and 50-54 are rejected under 35 U.S.C. 102(a) and 35.U.S.C 102(e)** as being anticipated by LaFleur et al (U.S. Patent No. 6,433,145 B1)

With respect to claim 2, LaFleur et al disclose a method for the specific modulation of the expression of target genes in cells and/or tissues of the eye, wherein a composition comprising one or more double-stranded oligoribonucleotides (dsRNA) is introduce into a cell, tissue or organism outside the blood-brain or blood-retina barrier (col. 9, line 52; col. 102, line 14).

With respect to claims 3 and 46, LaFleur et al disclose the method results in the provision of a test cell, tissue or organism, which can be preferably maintained under conditions allowing the degradation of the corresponding mRNA of one or more of target genes by RNA interference. An embodiment of the invention is an isolated cell or tissue of a subject or animal

model wherein the agent may be administered over a long-term period (col. 77, lines 29-30). Furthermore, the cells may be used to screen for KDI antagonists (col. 138, line 25).

With respect to claims 5-6, LaFleur et al disclose the dsRNA specifically modulates or inhibits target gene expression, wherein the target cellular mRNA may encode KDI (col. 140, lined 23).

With respect to claims 7-9, LaFleur et al disclose the cells and/or tissues are from the retina (col. 118, lines 35-37; col. 130, lines 37-46),

With respect to claim 10, LaFleur et al do not use the terms "retinal pigment epithelium" nor "neurosensory retina cells"; however, one of ordinary skill in the art readily understands that the retina tissue comprises "retinal pigment epithelium" and "neurosensory retina cells". Thus, the disclosure of LaFleur et al reasonably embraces such limitations, absent evidence to the contrary.

With respect to claim 13, LaFleur et al disclose the dsRNA molecules are at least 15 nucleotides, more preferably at least about 20 nucleotides (col. 15, lines 3-4; col. 17 lines 19-20). The antisense approach is used to inhibit translation of endogenous target gene mRNA, e.g. KDI, wherein the oligonucleotides range from about 6 to about 50 nucleotides in length (col. 141, lines 5-8, 15-17).

With respect to claims 19-20, LaFleur et al disclose the inventive nucleic acids may be inserted into vectors and operably linked to a tissue-specific promoter (col.s 75-76; col 101, lines 57-67; col. 140, lines 23-25).

With respect to claims 21-22 and 54, LaFleur et al disclose the dsRNA may be combined with one or more suitable carriers, wherein the carrier may be a liposome (col. 76, lines 25-32).

With respect to claims 24-25, LaFleur et al disclose that various delivery systems are known and can be used to administer a compound of the invention, e.g. encapsulation in liposome particles, intravenous or subcutaneous routes, e.g. topical drops and eyedrop form, wherein the composition may be provided by continuous subcutaneous infusion, or continuous infusion into the aqueous humor in order to increase the local concentration of the polynucleotide in the retina, wherein the carrier may be specific for the retinal cells, e.g. by targeting a specific receptor (col. 76, lines 25-40; col. 77, line 55; col. 79, lines 32-33).

With respect to claim 26, LaFleur et al disclose the agent may be administered by different routes, e.g. systemically injection or topically, e.g. as eyedrops (col. 107, line 19; col. 119, line 38).

With respect to claims 27-28 and 31, LaFleur et al disclose the subject may be human (col. 78, line 48).

With respect to claims 50-53, LaFleur et al disclose the polynucleotides of the invention may be used in the treatment of retinal diseases such as macular degeneration and retinoblastoma (col. 118, lines 35-37).

11. **Claims 2-13, 21-22, 24-28, 31, 46, 50 and 54 are rejected under 35 U.S.C. 102(a) and 35.U.S.C 102(e)** as being anticipated by King (U.S. 2002/0165158 A1).

With respect to claim 2, King discloses a method for the specific modulation of the expression of target genes in cells and/or tissues of the eye, wherein a composition comprising one or more double-stranded oligoribonucleotides (dsRNA) is introduce into a cell, tissue or organism outside the blood-brain or blood-retina barrier, wherein the preferred embodiment is retinal tissue (pg 1, [0009]).

With respect to claim 3, King discloses the method results in the provision of a test cell, tissue or organism, which can be preferably maintained under conditions allowing the degradation of the corresponding mRNA of one or more of target genes by RNA interference. An embodiment of the invention is an isolated cell or tissue of a subject or animal model (pg 4, [0039], [0060]; pg 5, [0081-82]), wherein the agent may be administered over a long-term period (pg 4, [0049]).

With respect to claims 4 and 46, King discloses the method provides for the identification or validation of the function of a gene and drug discovery, the method further comprising comparing the resulting phenotype produced in the test cell, tissue or organism with that of a suitable control, thus allowing information on the function of the gene to be gained. The method may be used to evaluate an agent, e.g. screening for an agent, the method comprising determining if the agent modulates the expression of a target gene (pg 5, [0075], [0082]). Abnormal expression levels in the subject are compared to a control (pg 5, [0066], [0084]).

With respect to claims 5-6, King discloses the dsRNA specifically modulates or inhibits target gene expression, wherein the target cellular mRNA may encode Protein Kinase C (PKC) isoforms or Retinoblastoma (Rb) (pg 1, [0006]; pg 3, [0026]).

With respect to claims 7-9, King discloses the agent is targeted to retinal tissue (pg 3, [0033]),

With respect to claim 10, King does not recite the terms "retinal pigment epithelium" nor "neurosensory retina cells"; however, one of ordinary skill in the art readily understands that the retina tissue comprises "retinal pigment epithelium" and "neurosensory retina cells". Thus, the disclosure of King reasonably embraces such limitations, absent evidence to the contrary.

With respect to claims 11-12, King does not dislose that PKCβ and/or Rb are predominantly expressed in retinal cells or tissues. However, at the time of the invention, one of ordinary skill in the art recognized that PKCβ and Rb are highly expressed in retinal cells.

With respect to claim 13, King discloses the dsRNA molecules are between about 20 to 25 nucleotides (pg 9, [0123]), specifically 21-23 nucleotides (pg 10, [0129]).

With respect to claim 19, King discloses the inventive nucleic acids may be inserted into vectors, wherein the expression of the nucleic acid is operably linked to a promoter (pg 2, [0017]; pg 3, [0025]; pg 17, [0192]).

With respect to claims 21-22 and 54, King discloses the dsRNA may be combined with one or more suitable carriers, wherein the carrier may be a liposome (pg 10, [0126]; pg 16, [0183-0194]; pg 18, [0202]).

With respect to claim 24, King discloses the carrier may comprise compounds that achieve controlled release (pg 17, [0191]), wherein the period over which the agent is administered can be long term (pg 3, [0036]).

With respect to claim 25, King discloses the carrier may be specific for the retinal cells, e.g. as eyedrops and/or liposomes tagged with antibodies against cell surface antigens of the target tissue (pg 10, [0124-0127]; pg 18, [0202]).

With respect to claim 26, King discloses the agent may be administered by different routes, e.g. intravenous or administered to the eye as eyedrops (pg 10, [0124-0127]).

With respect to claims 27-28 and 31, King discloses the subject may be human (pg 2, [0021]).

With respect to claim 50, King discloses the inhibition of the target gene expression is associated with retinal disease, e.g. ischemic retinopathy and retinopathy-of-prematurity, (pg 1, [0010], pg 4, [0059]).

12. **Claims 2, 5-10, 13, 19-22, 24-28, 31 and 48-54 are rejected under 35 U.S.C. 102(e)** as being anticipated by Tolentino et al (U.S. Patent No. 7,148,342 B2).

With respect to claim 2, Tolentino et al disclose a method for the specific modulation of the expression of target genes in cells and/or tissues of the eye, wherein a composition comprising one or more double-stranded oligoribonucleotides (dsRNA) is introduce into a cell, tissue or organism outside the blood-brain or blood-retina barrier, wherein the preferred embodiment is retinal tissue (pg 1, [0009]).

With respect to claims 5-6, King discloses the dsRNA specifically modulates or inhibits target gene expression, wherein the target cellular mRNA may encode VEGF, Flt-1 and Flk/KDR genes (col. 2, lines 45-47).

With respect to claims 7-9 and 50-53, Tolentino et al disclose the compositions of the invention are used for the treatment of retinal diseases such as age-related macular degeneration (col. 2, lines 47-50).

With respect to claim 10, Tolentino et al do not use the terms "retinal pigment epithelium" nor "neurosensory retina cells"; however, one of ordinary skill in the art readily understands that the retina tissue comprises "retinal pigment epithelium" and "neurosensory retina cells". Thus, the disclosure of Tolentino et al reasonably embraces such limitations, absent evidence to the contrary.

With respect to claim 13, Tolentino et al disclose the dsRNA molecules are less than 30 nucleotides, about 19 to about 25 nucleotides, e.g. 21-22 nucleotides (col. 2, lines 8, 25 and 57-58; col. 7, line 15).

With respect to claims 19-20, King discloses the inventive nucleic acids may be inserted into vectors, wherein the expression of the nucleic acid is operably linked to a promoter, e.g. a tissue-specific promoter (col. 9, lines 37-47).

With respect to claims 21-22 and 54, Tolentino et al disclose the dsRNA may be combined with one or more suitable carriers, wherein the carrier may be a liposome (col. 13, lines 37-50).

With respect to claim 24, King discloses the carrier may comprise compounds that achieve controlled release, wherein the period over which the agent is administered can be long term, e.g. osmotic pumps, pellets or suppositories (col. 15, lines 28-35).

With respect to claim 25, Tolentino et al disclose the carrier may comprise a ligand molecule that can target the carrier to a particular cell or tissue (col. 13, lines 56-58).

With respect to claim 26, Tolentino et al disclose the agent may be administered by different routes, e.g. regional or systemic, intravenous (col. 12, line 39; col. 15, lines 15-35).

With respect to claims 27-28 and 31, Tolentino et al disclose the subject may be human (col. 11, line 60).

With respect to claim 48, Tolentino et al disclose the dsRNA comprises two symmetrical 3' overhangs of two nucleotides in length (col. 5, lines 45-60).

With respect to claim 49, Tolentino et al disclose the 3' overhangs may be 2'-deoxythymidine (col. 6, line 3).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. **Claims 2-13, 19-22, 24-28, 31, 46 and 48-54 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Robinson et al (U.S. Patent No. 5,814,620) in view of LaFleur et al (U.S. 6,433,145 B1) and Tuschl et al (U.S. 2002/0086356 A1).

Determining the scope and contents of the prior art.

Robinson et al disclose a method for the specific modulation of the expression of target genes in cells and/or tissues of the eye, wherein a composition comprising one or more antisense oligoribonucleotides are introduce into a cell, tissue or organism outside the blood-brain or blood-retina barrier, wherein the preferred embodiment is retinal tissue. The method of the invention is used for the treatment of retinal diseases such as age-related macular degeneration (col. 2, lines 36-37; col. 11, lines 15-20). Robinson et al disclose the method yields a test organism maintained under conditions allowing the degradation of the corresponding target gene mRNA (col. 11, line 30-col. 12, lined 15). The antisense nucleic acids are from about 15 to about

25 nucleotides in length, and may be chemically modified (col. 3, line 45-col. 4, line 14). The antisense nucleic acids are targeted against a cellular gene such as VEGF, thereby inhibiting expression of VEGF in the retina (col. 4, lines 23-26), and may be administered to the patient, e.g. human, locally or systemically (col. 3, lines 35-37; col. 4, lines 35-42), wherein the formulation may comprise a carrier, e.g. a liposome (col. 9, line 13) and/or slow-release polymers (col. 11, line 13).

Robinson et al do not disclose:

i) the antisense nucleic acid is double-stranded RNA,

ii) the dsRNA nucleic acid is encoded by a vector,

iii) the dsRNA is operably linked to a tissue-specific promoter,

iv) the carrier is specific for the cells and/or tissues, and

v) the method is used in drug discovery or target gene validation.

However, at the time of the invention, LaFleur et al disclosed a method for the specific modulation of the expression of target genes in cells and/or tissues of the eye, wherein a composition comprising one or more double-stranded oligoribonucleotides (dsRNA) is introduced into a cell, tissue or organism outside the blood-brain or blood-retina barrier (col. 9, line 52; col. 102, line 14), wherein the method results in the provision of a test cell, tissue or organism, which can be preferably maintained under conditions allowing the degradation of the corresponding mRNA of one or more of target genes by RNA interference. An embodiment of the invention is an isolated cell or tissue of a subject or animal model wherein the agent may be administered over a long-term period (col. 77, lines 29-30). Furthermore, the cells may be used to screen for KDI antagonists (col. 138, line 25).

LaFleur et al disclose the dsRNA specifically modulates or inhibits target gene expression, wherein the target cellular mRNA may encode KDI (col. 140, lined 23), wherein the dsRNA molecules are at least 15 nucleotides, more preferably at least about 20 nucleotides (col. 15, lines 3-4; col. 17 lines 19-20). The antisense approach is used to inhibit translation of endogenous target gene mRNA, e.g. KDI, wherein the oligonucleotides range from about 6 to about 50 nucleotides in length (col. 141, lines 5-8, 15-17), wherein one or more nucleotide bases

may be modified (col. 9, lines 60-65; col. 141-142). The inventive nucleic acids may be inserted into vectors and operably linked to a tissue-specific promoter (col.s 75-76; col 101, lines 57-67; col. 140, lines 23-25) and/or may be combined with one or more suitable carriers, wherein the carrier may be a liposome (col. 76, lines 25-32). Various delivery systems are known and can be used to administer a compound of the invention, e.g. encapsulation in liposome particles, systemically by intravenous or subcutaneous routes, e.g. topical drops and eye drop form, wherein the composition may be provided by continuous subcutaneous infusion, or continuous infusion into the aqueous humor in order to increase the local concentration of the polynucleotide in the retina, wherein the carrier may be specific for the retinal cells, e.g. by targeting a specific receptor (col. 76, lines 25-40; col. 77, line 55; col. 79, lines 32-33; col. 107, line 19; col. 119, line 38). The polynucleotides of the invention may be used in the treatment of cells and/or tissues from the retina (col. 118, lines 35-37; col. 130, lines 37-46), e.g. retinal diseases such as macular degeneration and retinoblastoma (col. 118, lines 35-37).

Neither Robinson et al nor LaFleur et al disclose:

i) the method may be used for the identification or validation of the function of a gene,

ii) the target gene is expressed predominantly or specifically in the eye,

iii) the dsRNA contains two symmetrical 3' overhangs, and

iv) the dsRNA 3' overhangs are 2'-deoxythimidine.

However, at the time of the invention, Tuschl et al disclosed methods of using single-stranded and double-stranded RNA molecules to mediate gene-silencing of a target gene expression to examine the function of a gene, to assess whether an agent acts on a gene and to validate targets for drug discovery (pg 2, [0010]), wherein the phenotype of the test cell or organism is then observed and compared to that of an appropriate control cell or organism (pg 2, [0010-0011]). The single-stranded and double-stranded RNA molecules are about 21 to about 23 nucleotides, wherein both strands of the dsRNA have a 3' overhang of two nucleotides, wherein the 3' overhang nucleotides may be substituted for 2'-deoxythymidine (pg 5, [0055]). Tuschl et al disclose that any cellular gene, e.g. an oncogene or the mRNA of any protein associated with or causative of a disease or undesirable condition, can be targeted for degradation using gene-

silencing RNAs (pg 6, [0061]).

Ascertaining the differences between the prior art and the claims at issue.

LaFleur et al do not use the terms "retinal pigment epithelium" nor "neurosensory retina cells"; however, one of ordinary skill in the art readily understands that the retina tissue anatomically comprises "retinal pigment epithelium" and "neurosensory retina cells". Thus, the disclosure of LaFleur et al reasonably embraces such limitations, absent evidence to the contrary.

Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals, possessing advanced degrees, including M.D.'s and Ph.D.'s. They will be medical doctors, scientists, or engineers. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in designing, formulating and administering gene-silencing RNA nucleic acids to mammalian subjects, as well as anatomical and physiological knowledge of the circulatory and ocular organ systems. Therefore, the level of ordinary skill in this art is high.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute an antisense gene-silencing RNA as taught by Robinson et al with a double-stranded gene-silencing RNA as taught by LaFleur et al with a reasonable chance of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. One of ordinary skill in the art recognized that, in general, siRNAs and antisense oligonucleotides can be used to produce the same effect, albeit with different potencies and by different biochemical mechanisms. siRNAs and antisense oligonucleotides can both be used to inhibit gene expression *in vivo* or *in vitro*, via mRNA degradation or translation attenuation, and, thus, both types of nucleic acids may be used to prevent the expression of a gene in a cell (Tuschl et al). Thus, in this sense, siRNAs and

antisense oligonucleotides are art-recognized equivalents that may be used for the same purpose: reducing or inhibiting gene expression. (See for example MPEP §2144.06, SUBSTITUTING EQUIVALENTS KNOWN FOR THE SAME PURPOSE.) An artisan would be motivated to substitute gene-silencing antisense RNAs for gene-silencing dsRNA or a vector expressing a gene-silencing dsRNA because dsRNAs are extraordinarily powerful reagents for mediating gene silencing and are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments (see for example, Tuschl et al, Figures 8A and 8B).

It also would have been obvious to try administering a gene-silencing dsRNA targeted against a disease-causing gene that is predominantly or specifically expressed in the eye because "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipate success, it is likely that product not of innovation but of ordinary skill and common sense." At the time of the invention, those of ordinary skill in the art were well aware that gene-silencing dsRNAs may be designed to target a disease-causing mRNA for degradation. An artisan would be motivated to try administering a gene-silencing dsRNA targeted against a disease-causing gene that is predominantly or specifically expressed in the eye because the patient would be less likely to suffer from adverse, non-specific side effects due to off-target responses in non-retinal cells while simultaneously achieving degradation of the intended target gene, thereby treating the disease or disorder that the patient is suffering from.

It also would have been obvious to combine the method of inhibiting the expression of a target gene in a retinal cell to further provide for a test cell, tissue or organism from which to identify or validate the function of a gene with a reasonable chance of success because all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Furthermore, LaFleur et al and Tuschl et al disclose that methods of using gene-silencing RNAs may be used is gene and drug discovery and validation assay methods. An artisan would be motivated to use gene-silencing dsRNAs in gene and drug discovery and validation assay methods because it is technically easier and less costly to temporarily silence a

novel gene with a specific dsRNA than it is to generate a genetically-modified genomic loss-of-function cell, tissue or organism for each and every gene the artisan wishes to assay in the screening methods.

Thus, the invention as a whole is *prima facie* obvious.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. **Claims 2, 5-13, 21-22, 25-28, 31, 48 and 50-53 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting** as being unpatentable over claims

1, 5-6, 9, 16 and 96 of copending Application No. 10/511,657 (U.S. 2006/0003915 A1), as per the claim set filed November 16, 2007. Although the conflicting claims are not identical, they are not patentably distinct from each other because the intended use of the instantly claimed method is for the treatment of a retinal disorder (pg 2, ¶4; pg 4, lines 3-4) and the method steps of the co-pending application are the same as the instant application, specifically: administering an effective amount of a composition comprising a dsRNA between 21 and 23 nucleotides in length and a carrier, said dsRNA having a nucleotide sequence corresponding to mRNA of a target gene expressed in the eye and comprising a terminal 3' hydroxyl group, wherein the composition is administered outside the blood-retina barrier, e.g. systemically, and wherein the retinal disease includes age-related macular degeneration.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

15. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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PRIMARY EXAMINER